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Visible light-mediated radical fluoromethylation via halogen atom transfer activation of fluoroiodomethane†

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Incorporation of the fluoromethyl group can profoundly influence the physicochemical properties of organic molecules, offering a promising strategy for the discovery of novel pharmaceutical agents. Direct fluoromethylation of unfunctionalized C(sp²) centres can be achieved using fluoromethyl radicals, but current methods for their generation usually rely on the activation of non-commercial or expensive radical precursors via inefficient single electron transfer pathways, which limits their synthetic application. Here we report the development of a fluoromethylation strategy based on the generation of fluoromethyl radicals from commercially available fluoroiodomethane via halogen atom transfer. This mode of activation is orchestrated by visible light and tris(trimethylsilyl)silane, which serves as both a hydrogen- and halogen atom transfer reagent to facilitate the formation of C(sp³)-CH₂F bonds via a radical chain process. The utility of this metal- and photocatalyst-free transformation is demonstrated through the multicomponent synthesis of complex α -fluoromethyl amines and amino acid derivatives via radical addition to *in situ*-formed iminium ions, and the construction of β -fluoromethyl esters and amides from electron-deficient alkene acceptors. These complex fluoromethylated products, many of which are inaccessible via previously reported methods, may serve as useful building blocks or fragments in synthetic and medicinal chemistry both in academia and industry.

Introduction

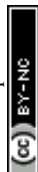
The prevalence of fluoroalkyl groups in pharmaceutical and agrochemical agents reflects their profound influence over the physicochemical and pharmacological properties of small organic molecules.^{1,2} Fluorine incorporation enables fine-tuning of lipophilicity, solubility, basicity, membrane permeability and metabolic stability,^{3–5} which has led to the broad application of fluoroalkyl groups as versatile bioisosteres in lead optimization.⁶ Moreover, rapid screening of fluorinated, sp³-rich fragment libraries via ¹⁹F NMR spectroscopy is an emerging strategy in fragment-based drug discovery.^{7–10} Novel synthetic methods for fluoroalkylation are, therefore, valuable tools for exploring new areas of fluorinated chemical space.^{11,12} In this context, diverse strategies to achieve trifluoromethylation^{13–21} and, increasingly, difluoromethylation^{22–28} have been established, while analogous monofluoromethylation^{29–31} processes remain under-developed. Nonetheless, the fluoromethyl (CH₂F) group is recognized as a pharmaceutically important motif, as evidenced by its presence in a number of lead compounds and approved drugs (Fig. 1a).²⁹

The fluoromethyl unit is primarily used as a bioisosteric replacement for methyl and hydroxymethyl groups,^{6,32} whereby the high electronegativity of fluorine and the strength of the carbon–fluorine bond can improve oral bioavailability, binding affinity, and metabolic stability. Alternatively, the α -fluoromethyl amine group, present in a class of amino acid-derived enzyme inhibitors (so-called suicide inhibitors), serves as a source of a fluoride leaving group during their mechanism of action.^{33,34} Considering the diverse and beneficial properties conferred by the fluoromethyl motif, exploration of novel fluoromethylated molecules constitutes a promising strategy for the discovery of new biologically active agents. To this end, the development of general and operationally simple methods for selective fluoromethylation remains a significant challenge in organofluorine chemistry.²⁹

In this context, various methods for nucleophilic, electrophilic, and metal-mediated fluoromethylation have been reported.^{29,35} Limitations of these reactions, however, include the use of auxiliary groups that require additional incorporation and removal steps, high loadings of metallic reagents, strong bases, and pre-functionalized substrates. Alternative and arguably more attractive strategies are centred on the generation of fluoromethyl radicals (Fig. 1b), which can directly engage in substitution,³⁶ addition,^{37–39} or cascade cyclization^{40–43} reactions at unfunctionalized C(sp) and C(sp²) centres. A pervasive feature of these methods is the use of radical precursors in

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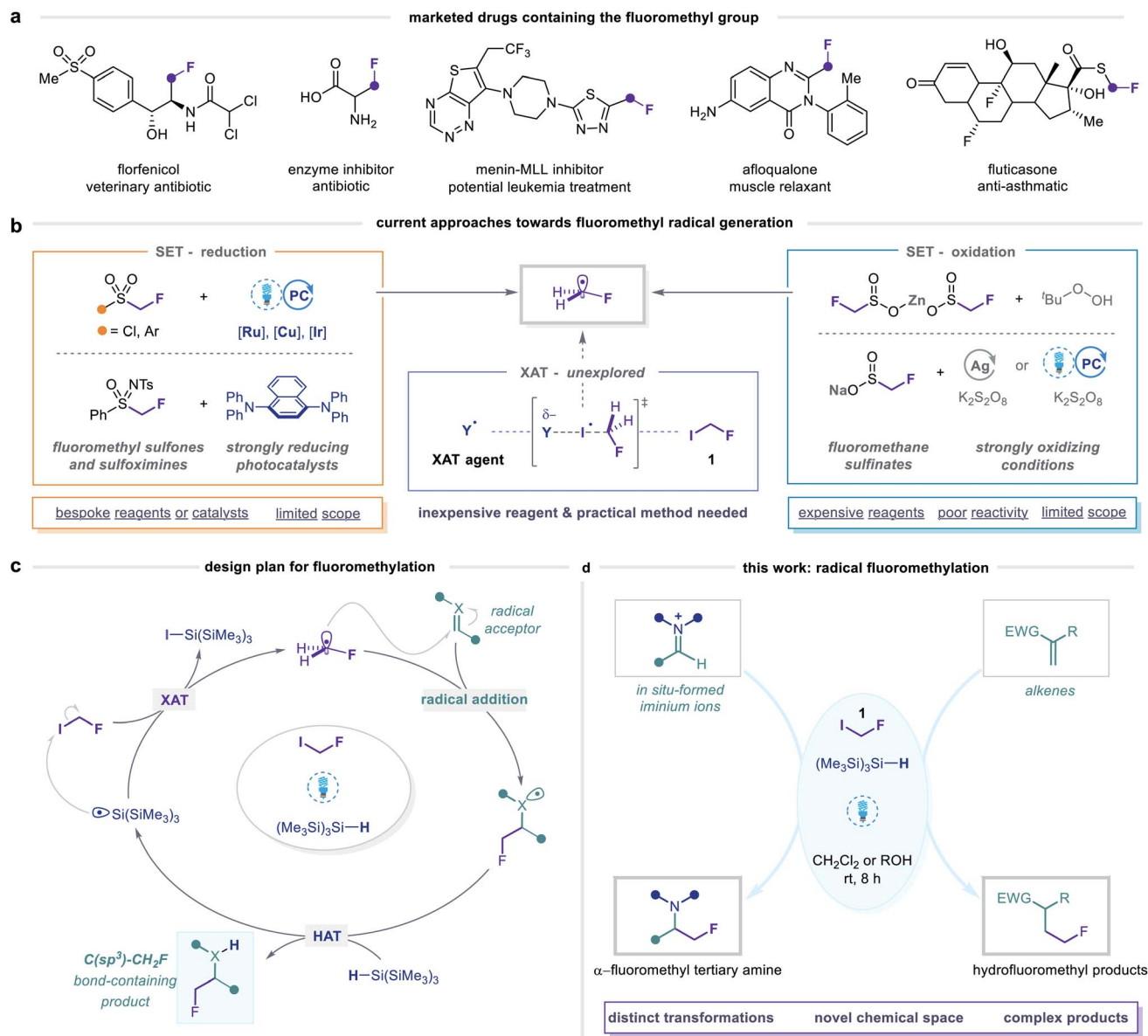


Fig. 1 Design plan for radical fluoromethylation *via* halogen atom transfer (XAT) activation of fluoroiodomethane. (a) The fluoromethyl motif is prevalent in pharmaceutical compounds. (b) Existing methods for radical fluoromethylation require expensive radical precursors, and strong oxidants or reductants, and are limited in scope. (c) Proposed XAT activation of fluoroiodomethane. (d) This work: application of XAT activation of fluoroiodomethane towards radical monofluoromethylation of unsaturated C=X bonds.

which the fluoromethyl group is bound to a sulfur atom, from which fluoromethyl radicals are generated *via* single-electron transfer (SET) pathways involving either reduction or oxidation at sulfur.⁴⁴ While this approach is analogous to that of many successful radical di- and trifluoromethylation strategies, its wider application for monofluoromethylation is limited by the higher cost, lower availability, and, in particular, reduced reactivity of the corresponding fluoromethylated reagents. The single-electron reduction of fluoromethyl sulfonyl derivatives is challenging due to their highly negative reduction potentials [E_{red} as low as -2.43 V *versus* saturated calomel electrode (SCE)].^{37,39–41} Therefore, methods employing these reagents require strong reductants, elevated temperatures, or bespoke

radical precursors, and exhibit limited scope. On the other hand, fluoromethanesulfinate salts undergo single-electron oxidation to generate fluoromethyl radicals,^{36,38,42,43} but display similarly limited reactivity, purportedly due to slow or poorly controlled radical generation from these species.^{38,45}

Given the limitations of these redox-active reagents, we sought to establish a radical fluoromethylation strategy comprising (i) a readily available radical precursor, (ii) a distinct mode of activation to generate fluoromethyl radicals, and (iii) the construction of previously intractable $C(sp^3)-CH_2F$ bond-containing products. For this purpose, we considered fluoroiodomethane **1**, a commercially available and easily handled liquid (bp 53 °C) that serves as a versatile source of the



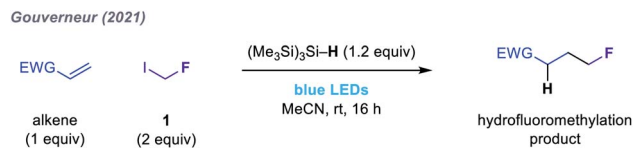


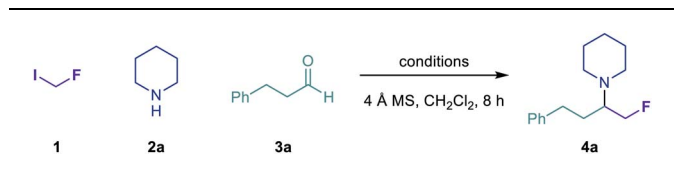
Fig. 2 Hydrofluoromethylation of electron-deficient olefins using **1**.⁴⁹

fluoromethyl group in many two-electron processes.⁴⁶ Despite these attractive features, the use of **1** as fluoromethyl radical precursor had been, until very recently, limited to a solitary report from 1975 in which gas-phase mixtures of **1** and simple olefins were photolyzed using ultraviolet (UV) light to form complex mixtures of substitution products in low conversions.⁴⁷ The lack of synthetic application of **1** using single-electron (photo)redox chemistry reflects its highly negative reduction potential ($E_{\text{red}} < -2$ V versus SCE) which would necessitate the use of strongly reducing reagents or photocatalysts. To circumvent this inherent redox requirement of radical generation *via* SET, we proposed that homolytic cleavage of the carbon-iodine bond in **1** could be achieved *via* a halogen atom transfer (XAT) pathway (Fig. 1b and c). We hypothesised that visible light irradiation of **1** and a suitable XAT-agent precursor, namely tris(trimethylsilyl)silane [(Me₃Si)₃Si-H],⁴⁸ would orchestrate the generation of fluoromethyl radicals and facilitate their polarity-matched addition to electron-deficient C(sp²) centres (Fig. 1c and d). A key feature of this proposed strategy is the multi-faceted role played by (Me₃Si)₃Si-H: following fluoromethyl radical addition to the acceptor, (Me₃Si)₃Si-H intercepts the intermediate radical in a hydrogen atom transfer (HAT) step that forms both the desired fluoromethylated product and a (Me₃Si)₃Si· radical; subsequent XAT between this silicon-centred radical and a molecule of **1** generates another fluoromethyl radical to establish a chain process. During the preparation of this manuscript, Gouverneur and co-workers reported a similar visible light-mediated fluoromethylation process, using **1**, to affect the corresponding variant of the Giese reaction (Fig. 2).⁴⁹ Here, we report the successful realization of our design concept through the complementary development and implementation of a visible light-mediated strategy for the radical fluoromethylation of iminium ions to form α -fluoromethyl alkylamines. The multicomponent carbonyl fluoromethylative amination reaction affords complex fluoromethylated amine products that occupy previously under-explored areas of chemical space, and which should serve as valuable fluorinated building blocks to practitioners of synthetic and medicinal chemistry. We also detail that our protocol enables addition of the fluoromethyl group to electron-deficient alkenes to form β -fluoromethyl esters and amides, which demonstrates the wider capability of the visible light-mediated activation mode for the fluoromethyl radical.

Results and discussion

Our group recently reported a general method for the multicomponent synthesis of α -branched tertiary alkylamines,

Table 1 Selected optimization data for the carbonyl fluoromethylative amination reaction



Entry	Initiation method	HAT reagent	Additive	Yield ^a (%)
1	40 W blue LED	(Me ₃ Si) ₃ Si-H	—	<5
2	40 W blue LED	(Me ₃ Si) ₃ Si-H	TMS-Cl	30
3	40 W blue LED	(Me ₃ Si) ₃ Si-H	TMS-OTf	94
4	40 W blue LED	(Me ₃ Si) ₃ Si-H	TBS-OTf	95 (86)
5	50 °C, air atm	(Me ₃ Si) ₃ Si-H	TBS-OTf	0
6	70 °C, AIBN	(Me ₃ Si) ₃ Si-H	TBS-OTf	77
7	70 °C, AIBN	Bu ₃ Sn-H	TBS-OTf	0
8	40 W blue LED	(Et ₃ Si) ₃ Si-H	TBS-OTf	52
9	40 W blue LED	Et ₃ Si-H	TBS-OTf	0
10	40 W blue LED	Ph ₃ Si-H	TBS-OTf	0
11	40 W blue LED	PhSiH ₃	TBS-OTf	0

^a Yields determined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as internal standard. Isolated yield given in parentheses.

comprising the addition of alkyl radicals to iminium ions generated *in situ* *via* condensation of aldehydes and secondary amines.⁵⁰ Further development of this carbonyl alkylative amination (CAA) strategy using fluoromethyl radicals would enable the modular construction of α -fluoromethyl tertiary alkylamines, a pharmaceutically relevant class of amines for which no direct, general synthetic strategies have been reported. Our initial investigations to address this synthetic need focused on the carbonyl fluoromethylative amination reaction between fluoroiodomethane **1**, piperidine **2a** and hydrocinnamaldehyde **3a** (Table 1).

Visible light irradiation of **1** (3 equiv.), **2a** (1 equiv.) and **3a** (2 equiv.) in the presence of (Me₃Si)₃Si-H (2 equiv.) and 4 Å molecular sieves (MS) in CH₂Cl₂ for 8 h formed only trace amounts of the desired amine **4a**, as determined by ¹H NMR spectroscopy (entry 1). Evaluation of Lewis acid additives to promote formation of the iminium ion acceptor in high concentration revealed both *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBS-OTf) and trimethylsilyl trifluoromethanesulfonate (TMS-OTf) to be more effective than trimethylsilyl chloride (TMS-Cl), affording **4a** in near-quantitative assay yield (entries 2–4). We also assessed a number of alternative initiation methods and HAT reagents for the synthesis of **4a** (entries 5–11).⁵¹ In all cases, these proved inferior to the combination of visible light and (Me₃Si)₃Si-H, although the reaction proceeded in good yield under thermal initiation using azobisisobutyronitrile (AIBN) and (Me₃Si)₃Si-H (entry 6). Ultimately, the conditions outlined in entry 4 were found to be optimal, affording **4a** in 86% isolated yield.

Having identified suitable conditions for the carbonyl fluoromethylative amination reaction, we evaluated the scope of the transformation with respect to other cyclic secondary alkylamines (Fig. 3). A variety of functionalized cyclic and



heterocyclic secondary alkylamines could be used in the reaction with aldehyde **3a**, affording the α -fluoromethyl cyclic tertiary alkylamines **4a–4h** in good yields. Notably, tertiary alkylamines of this type are not readily accessible *via* nucleophilic fluoromethylation strategies which require auxiliary-activated imines.⁵² Acyclic secondary alkylamines containing a variety of linear and branched alkyl substituents, as well as

ester, nitrile, hydroxyl and heteroaromatic functionality, also reacted efficiently to give amines **4i–4s**. In addition to these manipulable and medically important motifs, the *N*-benzyl group in amines **4k–4s** provides a useful handle for their deprotection and further elaboration. For *N*-alkyl anilines and diarylamines, reductive amination was observed as a competing side reaction, although the desired α -fluoromethylated amine

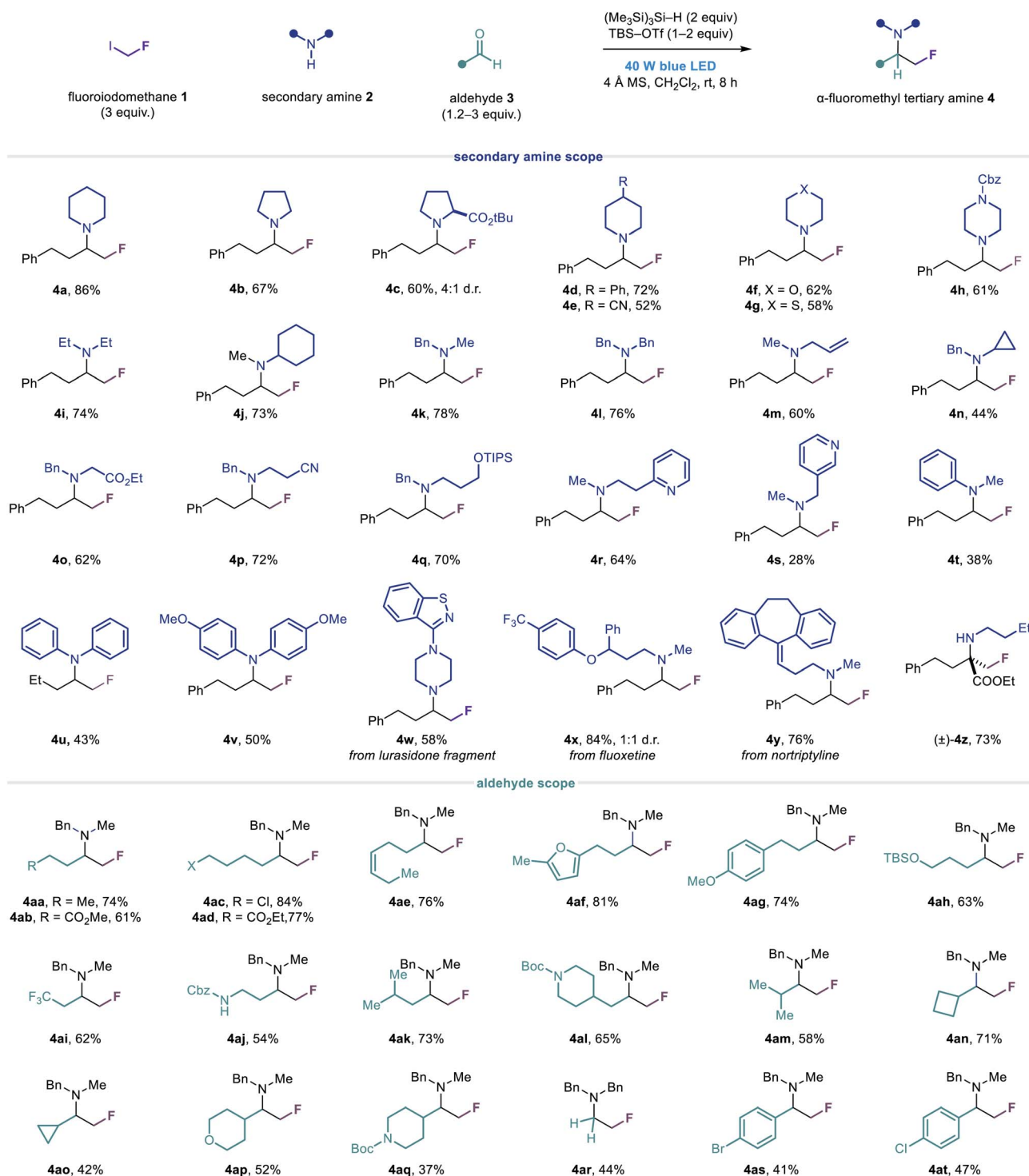
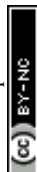


Fig. 3 Scope of the carbonyl fluoromethylative amination reaction.



products **4t–4v** could generally be obtained in synthetically useful yields.

The reaction was amenable to the functionalization of several secondary amine drugs and drug fragments, affording their α -fluoromethyl tertiary amine derivatives **4w–4y** in moderate to excellent yields. Considering the significant and predictable effect that β -fluorine incorporation has on reducing the basicity of amines, this transformation may prove useful for the development of novel pharmaceutical agents and the modulation of their biological properties.

To further demonstrate the utility of our novel fluoromethylation strategy, we employed **1** with iminium ions derived from *n*-butylamine and ethyl 2-oxo-4-phenylbutanoate (an α -keto ester) to generate α -fluoromethyl α -tertiary amino acid derivative **4z** in good yield.⁵³ Compounds such as **4z** are structural analogues of a class of biologically important α -fluoromethyl α -amino acid decarboxylase inhibitors (Fig. 1a), which are generally synthesized *via* linear, multi-step routes. Conversely, these α -fluoromethyl α -tertiary amino esters can easily be synthesized in one step from readily available precursors, exemplifying the rapid access to structural diversity that this modular approach can provide.

Next, we assessed the scope of the aldehyde component, using *N*-methylbenzylamine **2k** and diversely functionalized linear and β -branched aldehydes to prepare the α -fluoromethyl tertiary alkylamines **4aa–4al**. We found that the greater steric demand imposed by α -branched aldehydes generally led to slightly diminished yields of the corresponding amines **4am–4aq**, although this could be mitigated by using additional equivalents of aldehyde in some cases. Notably, amine **2k** exhibited sufficient reactivity in the absence of TBS-OTf to

enable the synthesis of tertiary alkylamine products containing acid-sensitive functional groups such as the *tert*-butyloxycarbonyl (Boc) group (**4al** and **4aq**). A reaction employing paraformaldehyde and dibenzylamine afforded unbranched tertiary fluoroethylamine **4ar** in modest yield. Substituted benzaldehydes could also be tolerated, giving α -fluoromethyl tertiary amines **4as** and **4at**, albeit in low yields, which are suitably functionalized for downstream cross-coupling reactions.

In our efforts to develop a general fluoromethylation strategy, we sought to engage electrophilic species other than iminium ions in reactions with fluoromethyl radicals. We reasoned that our newly developed fluoromethylation strategy would be suitable for the direct hydrofluoromethylation of electron-deficient olefins *via* radical conjugate addition followed by rapid HAT from $(\text{Me}_3\text{Si})_3\text{Si-H}$. Notably, although the addition of fluoromethyl radicals to acrylamides or acrylates is the elementary step in several previously reported fluoromethylation strategies (Fig. 1b), to the best of our knowledge, simple reduction of the resulting radical intermediates (*via* either HAT or SET/proton transfer) has not been reported; instead, these species are typically involved in subsequent migration, cyclization or atom transfer processes. Using slightly modified reaction conditions, a range of electron-deficient olefins were subjected to the novel hydrofluoromethylation reaction (Fig. 4). Simple acrylamides and acrylates, as well as maleimide **5g**, reacted efficiently, affording the corresponding β -fluoromethyl carbonyl products **6a–6g**. Phenyl vinyl sulfone was also readily functionalized, affording **6h** in good yield. Vinyl phosphonate and vinyl ketone substrates were less well tolerated, affording **6i** and **6j** in modest assay yields. While less

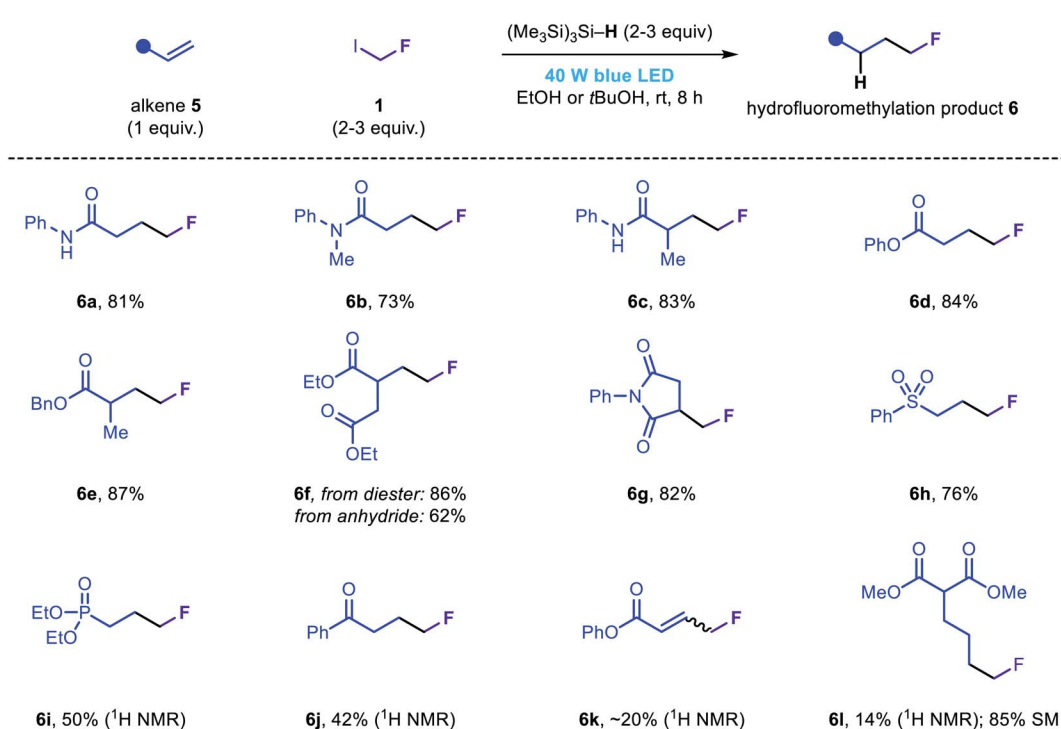


Fig. 4 Scope of the hydrofluoromethylation of electron-deficient olefins.



efficient, hydrofluoromethylation of phenyl propiolate and an unactivated terminal alkene (**5l**) to afford **6k** and **6l** demonstrated the hydrofluoromethylation of more diverse unsaturated acceptors.

Conclusions

In summary, we have developed a novel visible light-mediated method for the monofluoromethylation of unsaturated carbon-carbon/heteroatom bonds (C=X bond, X = carbon or nitrogen) by addition of fluoromethyl radicals. In contrast to previously reported methods, the fluoromethyl radical is generated *via* halogen atom abstraction from commercially available fluoriodomethane by a stable silyl radical. This light-mediated process underpins a modular strategy in which commercially available amines, aldehydes and fluoriodomethane are combined to access synthetically complex α -fluoromethylated tertiary amines. Critically, the reaction features a vast scope and excellent functional group tolerance, including highly elaborate drug scaffolds and other biologically relevant structures such as α -fluoromethyl α -tertiary amino esters. The synthetic utility of this new method is also demonstrated in a hydrofluoromethylation reaction of electron-deficient olefins to obtain C(sp³)-C(sp³) coupled fluoromethylated products. Given the intuitive retrosynthetic logic underpinning the carbonyl fluoromethylative amination and hydrofluoromethylation reactions, we hope they may be rapidly adopted in academic and industrial laboratories alike.

Data availability

Data associated with this article, including experimental procedures and compound characterization, are available in the ESI.†

Author contributions

M. J. G., R. K. and P. J. D. conceived the project. P. J. D. and R. K. conducted the experiments. P. J. D., R. K. and M. J. G. analyzed the experiments. P. J. D., R. K. and M. J. G. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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